#28 Decl. w/attach. 9/19/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Brian R. Murphy, et al.

Application No.: 09/083,793

Filed: May 22, 1998

For: PRODUCTION OF ATTENUATED PARAINFLUENZA VIRUS FROM CLONED NUCLEOTIDE SEQUENCES

Examiner: M. Mosher

Group Art Unit: 1648

DECLARATION OF BRIAN R. MURPY UNDER 37 CFR 1.132

DATE OF DEPOSIT: August 26, 2002

I HEREBY CERTIFY THAT THIS PAPER IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL, POSTAGE PREPAID ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231.

TYPED NAME: Jeffrey J. King
REGISTRATION NO.: 38,515

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Brian R. Murphy, M.D., declare as follows:

1. I am presently employed as co-head of the Laboratory of Infectious Diseases within the National Institute for Allergies and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). I have been directly involved with this laboratory for over thirty years, beginning with my initial post as a research physician studying respiratory viral diseases in 1970. My Curriculum Vitae and Bibliography of publications are attached.

2. As current head of the respiratory virus section within NIAID, I oversee the research activities of more than 25 research professionals within the section. For approximately 17 years, our efforts have focused on vaccine development for parainfluenza virus (PIV).

3. I have read and fully understand the specification and claims of the above-identified patent application, on which I am a co-inventor.

4. I have reviewed and carefully considered the substantive Office Actions (identified as Papers No. 10, 17, and 22) presented in the above-identified application.

5. I have carefully reviewed the Belshe et al. reference (U.S. Patent No. 5,869,036) cited in the above-noted Office Actions.

6. The facts presented and discussed below are directed to two principal issues raised in the current Office Action (Paper No. 22): (1) Does the Belshe et al. specification cited by the Office teach or suggest the subject matter as recited in the rejected claims of the current application? And (2) Does the current application teach how to make and use the subject matter set forth in the pending claims without undue experimentation considering the level of predictability in the art?

7. Considering all of the facts presented in the record, as discussed herein below, I conclude that the Belshe et al. patent (alternatively, the '036 patent) does not provide sufficient description and guidance to permit a person of ordinary skill in the art (at either the time the Belshe et al. patent or the current application was filed) to recover a recombinant parainfluenza virus (PIV) from cDNA. On the contrary, the Belshe et al. specification only hypothetically discusses the possibility of recovering a recombinant PIV from cDNA. No such cDNA nor recombinant PIV is actually described in structural terms that would qualify as a "written description" of such materials, and it is apparent that no "working example" of a cDNA encoding a recombinant PIV, nor of an actual recombinant PIV, is provided by the Belshe et al. disclosure. Additionally, considering the level of predictability in the art prior to the discoveries presented in the instant application, the teachings of Belshe et al. would not have been considered to provide an "enabling" disclosure of the presently claimed invention. That is to say, Belshe et al. offer such limited direction and guidance that, even when supplemented by available knowledge in the art at the time the instant application was filed, the skilled artisan would not have considered the public to be placed "in possession of" a recombinant PIV produced from cDNA. This conclusion, and the related conclusions below, relate to the fundamental technology of the present invention, i.e., successful recovery of a viable, self-replicating, recombinant PIV from cDNA. It is even more clear that certain detailed aspects of the invention, e.g., involving identification and manipulation of attenuating mutations and their introduction, singly and in combination, into a recombinant PIV, and

successful recovery of chimeric PIVs, and attenuated chimeric PIVs, are neither disclosed nor suggested by Belshe et al.

8. Considering the specific issue of "obviousness" raised by the Office, I conclude that the limited teachings of Belshe et al. fail to provide a practical suggestion or motivation that would have led the skilled artisan to undertake production of a recombinant PIV from cDNA with a "reasonable expectation of success". Considering the poorly developed state of knowledge and high degree of unpredictability in the art, among other technical challenges discussed below, to achieve this goal without the benefit of the instant disclosure would have been viewed by the skilled artisan as requiring such extensive and uncertain experimentation that would have been characterized as "undue" experimentation--unattended by a "reasonable expectation of success". The same facts, set forth below, that support this conclusion also point to a conclusion that the instant disclosure provides "unexpected results" in the successful production of a recombinant PIV from cDNA. Concerning more detailed aspects of the invention, the results provided by the instant disclosure allow production of singly and multiply attenuated, recombinant PIVs, chimeric PIVs, and attenuated chimeric PIVs, that are sufficiently infectious in a mammalian host to generate a desired immune response yet are suitably attenuated for selection and development as PIV vaccine candidates. That these novel results were achieved within the instant invention was even more surprising that the basic recovery of recombinant PIV, based on the limited teachings of Belshe et al. combined with general knowledge in the art at the time of the invention.

9. With respect to the issue of enablement newly raised by the Office, I conclude that the present disclosure provides sufficient description and guidance to enable the skilled artisan to practice the invention in a manner fully commensurate with the scope of the claims presented for review. In particular, the application details materials and methods and provides extensive working examples that teach how to make and use recombinant PIVs from cDNA--in a manner that correlates reasonably with the full breadth of the claims. Numerous recombinant PIVs having representative modifications, such as a chimeric construction and/or single and multiple attenuating mutations, are provided. These examples constitute a representative assemblage of species commensurate with the full scope of the claims. These representative species are shown by detailed, *in vitro* and *in vivo* working examples to have the desired characteristics for use as vaccine candidates. As stated previously in the record, prior to the instant invention such materials and methods would have been considered highly unpredictable. This unpredictability does not, however, translate to the presently claimed invention that

was achieved through an exhaustive, successful research campaign culminating in the instant disclosure. Following this detailed disclosure, the artisan can now readily undertake production and selection of additional operable species within the claims, and thereby practice the invention commensurate with the full scope of the claims without "undue experimentation". This is true even though certain species that fall within the claims may be sub-optimal or even inoperable for vaccine production.

10. Turning now to the facts of record that support the foregoing conclusions, the Belshe et al. specification fails to provide a single example of a recombinant PIV recovered from a cDNA. On the contrary, the Belshe et al. reference is limited in its teachings to a purported *in vitro* complementation assay described to evaluate temperature sensitivity. This limited study is attended by fundamental flaws in its design and interpretation, as discussed below. Even if the Belshe et al. complementation assay results are accepted as reported, there is no theoretical or empirical basis to extrapolate these findings into the context of a complete, infectious virus and, most importantly, to the production of a recombinant PIV that is viable, attenuated, and immunogenic *in vivo*.

11. In contrast to the deficient teachings of Belshe et al., the instant application provides detailed working examples that detail production and employment of cDNAs to yield successful recovery of (1) recombinant wild type human parainfluenza virus type 3 (PIV3); (2) multiple recombinant PIV3s containing well defined single attenuating mutations; (3) multiple recombinant PIV3s containing more than one attenuating mutation in combination; (4) a chimeric PIV3-1 virus in which the HN and F open reading frames (ORFs) of wild type PIV3 were replaced with ORFs encoding the counterpart HN and F proteins of PIV1; and (5) viable, immunogenic derivatives of chimeric PIV3-1 having defined attenuating mutations incorporated in the chimeric virus.

12. Belshe describes a simple, *in vitro* complementation assay in which a plasmid expressing a wild type L protein in a transfected cell monolayer reportedly increased the level of replication of PIV3 cp45 from10^{1} (Table 1 in the Belshe patent) to $10^{2.3}$ PFU/ml (Table 2 in the Belshe patent) at 39.5°C. Importantly, a control plasmid containing the cp45 mutations was not evaluated in this complementation assay, and thus the difference identified in the complementation assay cannot be ascribed to the sequence differences between the wild type and cp45 PIV3 L protein. In addition, the L cDNA employed by Belshe et al. was not evaluated for its effect on replication of wild type HPIV3. This is a critical control that would address the very real possibility that the modest increase in virus replication was simply due to increased expression of L protein, which is expressed at very low levels during virus infection. Thus, the increase may reflect a "dose effect" rather than true complementation

of a *ts* defect. The assay of Belshe et al. (see Table 3) is also unreliable in other crucial aspects. For example, complementation with L and P reportedly yielded 190 infectious virus particles. The further inclusion of NP reportedly yielded 2,300 plaque forming units (pfu), a 12-fold increase that, by the logic of the assay, would seem significant and would reasonably be interpreted as evidence that cp45 NP must contain one or more critical temperature sensitive or attenuation mutations. Yet, the sequence information provided in Fig. 1 of Belshe et al. indicates that cp45 NP does not contain a single mutation compared to wild type. Thus, the purported positive results in the complementation assay contain internal inconsistencies and lack the essential verification of important experimental controls. This determination would have been clear to the skilled artisan and would have detracted significantly from the motivation provided by the cited reference and the expectation of success that the artisan would have to practice the presently claimed invention as allegedly taught or suggested by Belshe et al.

13. The 20-fold increase in replication of cp45 at 39.5°C in the presence of L reported by Belshe et al. was interpreted as indicating that the mutations in the L protein of cp45 specify an attenuation phenotype. It is important, however, to place the complementation findings reported by Belshe et al. in appropriate scientific context. A typical yield of wild type HPIV3 from 3 X 10^6 cells (as in the experiment of Belshe et al.) would be expected to be 5 X 10^8 pfu or more, such that each cell produces more than 100 pfu. The complementation assay of Belshe with L alone yielded 330 pfu for the entire culture. This suggests that as few at 3 or 4 cells (and certainly no more than 330 cells) successfully produced virus, whereas the remaining several million failed to produce a single particle. Hence, even if the complementation is accepted as authentic, it is of such a low efficiency that its significance is highly doubtful. In any case, there are no means for extrapolating findings from such a complementation assay to infectious virus. Thus, the 20-fold increase in the replication seen in the complementation assay cannot be extrapolated to predict or understand the magnitude of the contribution of the L protein mutations to the ts phenotype of cp45, nor what the biological properties of a hybrid virus carrying only these mutations might be. At best, the findings are simply suggestive that the L gene mutations might contribute to some undefined portion of the temperature sensitivity of the cp45 virus. Furthermore, and most importantly, the complementation assay of Belshe relates only to the *ts* phenotype of cp45, and does not address the attenuation phenotype *in vitro* or *in vivo*. While a *ts* phenotype often is associated with attenuation, it is not possible to predict that attenuation will indeed result, nor what its magnitude might be. This is a critical deficiency, since the level of attenuation *in vivo* is essential to assess the safety of a vaccine virus. Only by actually making an infectious recombinant virus, as provided in multiple working examples in the present disclosure, can one assess

the *in vivo* attenuation of the virus to determine its usefulness as a vaccine candidate. Again, each of these deficiencies of Belshe et al. would have been clear to the skilled artisan and would have undermined the motivation and expectation of success for practicing the claimed invention following the teachings of Belshe et al.

14. Only with the aid of the present disclosure providing a successful cDNA recovery system can the phenotypic effect of any desired mutation (e.g., an attenuating mutation from PIV3 cp45) be evaluated and demonstrated. For example the instant disclosure demonstrates that a ts mutation identified in L can be segregated from complementary or interactive effects of other cp45 mutations. In this context, it is critical for evaluating the speculative teachings of Belshe et al. that at least a representative set of mutations identified and segregated into a viable recombinant vaccine candidate be verified as attenuating, and that such attenuation be balanced sufficiently to yield a protective immune response in susceptible hosts. The simple studies of Belshe et al. were limited to complementation of replication for a cp45 virus using a wild type L plasmid. These studies were only conducted *in vitro* using tissue culture cells, and were not validated by parallel studies *in vivo*. In this context, it was quite possible that recombinant viruses incorporating one or more of the three "temperature sensitive" (ts) mutations in the cp45 L gene mutations would not be attenuating (att) *in vivo*. In particular, a finding that replication of cp45 may be complemented by wild type L protein in tissue culture cells is not clearly predictive that a virus bearing one or more of these mutations would be attenuated *in vivo*. This correlative deficiency is apparent from the following considerations. As an initial point, it is known that entire classes of viruses called "temperature-dependent hose range (td-hr) mutants" may be ts on one tissue but not on other tissue culture cells. These td-hr mutants are not necessarily attenuated *in vivo* (see Snyder et al., Virus Research 15:69-84, 1990 and Shimizu et al., Virology 124:35-44, 1983). As described in Snyder et al., an exemplary mutant (clone 143-1) of influenza virus was shown to be highly ts in tissue culture cells, but was not significantly attenuated *in vivo*. Additional findings by Shimizu et al. indicate that such td-hr mutants are common and are found in many different complementation groups of the influenza virus (i.e., they are present in many different genes of the virus). The Belshe et al. reference does not demonstrate whether any of the contemplated ts mutations in the L gene of cp45 belong in the td-hr class of mutations or in the other class of ts mutations whose replication is effected by the temperature present in the host animal. In view of this deficiency, the simple description of a complementation phenotype for a group of multiple, unsegregated mutations in a complete gene *in vitro* does not serve as a reliable indicator of attenuation *in vivo*. As detailed herein, the instant disclosure provides the basic tools, along with fully detailed description and guidance, to resolve these deficiencies

and enable the skilled artisan to practice the invention throughout the scope of the claims presented for review.

15. I further note that the sequence of the cp45 L gene claimed by Belshe was taken directly from published work by others in our laboratory in 1993 (Stokes et al, 1993 Virus Research 30:43). Thus, the mutations in L evaluated by Belshe were already described in the literature and were considered possible attenuating mutations. In this context, the Belshe et al. disclosure provided little new information on the nature of the genetic determinants of the ts phenotype of cp45--only following previous suggestions that one or more mutations in L might specify some portion of the ts phenotype in cp45. In contrast, by describing successful recovery of recombinant PIV from cDNA, and by further incorporating individual and combinatorial mutations from cp45 (from several genes as well as from extragenic portions of the genome) in recombinant PIVs, the instant disclosure dissects and maps out the specific contributions of the individual lesions in cp45 to the attenuation phenotype. Following introduction of these various, representative mutations, singly and in combination, into recombinant PIVs, the ability to achieve an attenuation phenotype using various manipulations, and to fine tune the attenuation phenotype to achieve useful vaccine strains, was established using widely accepted *in vivo* models for attenuation and immunogenic activity in humans.

16. The sequences of the PIV3 cp45 virus reported by Belshe et al. rely completely on the published sequences of others (Stokes et al, 1993 Virus Research 30:43), as noted above, and it is important to consider that those sequences were subsequently found to contain errors that were corrected by the present disclosure. The complete, correct sequence of cp45 is presented in current specification. This information, combined with the first successful attempt to generate recombinant PIVs containing various combinations of these mutations, defined the major attenuating mutations in PIV3 cp45 to be in the genes encoding not only the L protein, but also the C and F proteins. The present work also provided the first analyses of virus replication, immunogenicity and protective efficacy for these single and combinatorial mutants in accepted models for PIV infection and vaccine development. Examination of Figure 1 of the Belshe et al. patent fails to identify the mutation in C. The Figure only reiterates the incomplete sequence information and analysis previously reported by Stokes et al. From Belshe et al., one would not know that the F or C mutations present in cp45 were attenuating mutations, and that these mutations are useful in cDNA-derived recombinant vaccine viruses. The materials and methods described in the instant disclosure not only identified the attenuating mutations present in cp45, but provided a general method that later proved useful in identifying other attenuating mutations present in

heterologous viruses such as a mutation designated 456 from the respiratory syncitial virus (RSV) L protein, a mutation designated 170 from the Sendai virus C protein, and a mutation designated 1711 mutation from the L protein of bovine PIV3 (BPIV3), for incorporation into recombinant PIVs of the invention (data will be provided if requested by the Office).

17. As noted above, recovery of a recombinant virus from cDNA was not accomplished by Belshe et al. Nontheless, the reference speculates even further concerning the prospect of hybrid (chimeric) recombinant vaccine viruses (Example 7), and such recombinant viruses are referred to in multiple claims of Belshe et al. However, the reference clearly fails to describe or enable any chimeric cDNA constructs or methods for recovering chimeric viruses from cDNA, nor to characterize any chimeric viruses *in vitro* or *in vivo* for identification of useful vaccine candidates. Thus, although the principal disclosure of Belshe et al. purports to render construction of chimeric PIV and other "hybrid" viruses possible, the reference neither describes, teaches nor suggests the presently claimed subject matter. On the contrary, no specific guidance is provided to enable any kind of cDNA recovery of PIV, much less recovery of a viable, attenuated and infectious chimeric PIV as provided by the instant disclosure. The speculative teachings of Belshe et al. would not have been accepted by the skilled artisan as providing a clear teaching or practical motivation to achieve the presently claimed invention. This conclusion is underscored by the vast diversity of viral "targets" contemplated by Belshe et al. for constructing "hybrid" viruses, as indicated by the following passage:

> Hence, in addition to related enveloped, negative-sense, single-stranded RNA viruses such as human parainfluenza virus type 1 (HPIV-1), human parainfluenza virus type 2 (HPIV-2), respiratory syncytial virus (RSV), human influenza virus type A, human influenza virus type B, and measles viruses, target viruses would also include other enveloped viruses, such as paramyxoviruses, orthomyxoviruses, retroviruses (e.g. human immunodeficiency viruses HIV-GP120 and HIV-GP41), arenaviruses, coronaviruses, bunyaviruses, rhabdoviruses, togaviruses, herpesviruses, poxviruses and hepadnaviruses. Preferable target viruses include enveloped viruses which reproduce in the cytoplasm. The target virus of the present invention may be specific to humans, specific to animals or common to both animals and humans. Bovine RSV and cattle HPIV-3 (shipping fever virus) are typical animal viruses included within the scope of the present invention. [Col. 8, lines 42-58, underscore added.]

In contrast to these broad, prophetic and overreaching statements, the present specification provides detailed description and guidance, as well as a fully representative assemblage of working examples

(e.g., various attenuated PIV3-1 chimeric vaccine candidates) that is fully commensurate with the scope of claims presented for review.

18. The differences between the present disclosure and the Belshe et al. reference relating to the description of a system to recover infectious replicating viruses from cDNA for selection as vaccine candidates are outlined in Tables 1–3 below, and are briefly addressed in the following paragraphs.

Table 1 – Comparison of PIV3 and of chimeric PIV3 cDNA constructs used to rescue viable virus

Requirements for successful rescue of recombinant PIV3 and of chimeric PIV3 virus	Described in Murphy 09/083,793	Described in Belshe 5,869,036
Characteristics of PIV3 cDNA a- Viable (free of errors) PIV3 sequence b- specified length ("rule of six"[described below]) c- sequence that specifies a virus capable of being recovered and capable of efficient replication in cell culture and animals d- Structure of the expression plasmid into which PIV3 sequences are placed, strategy for producing correct 3′ and 5′ ends, and conditions for stable propagation in bacteria	Complete description of viable sequence and construction of cDNAs and expression plasmids from which PIV3 was recovered (confirming authenticity of sequence and effectiveness of recovery conditions); efficient replication of recovered virus in vitro and in vivo	Sequence of cDNA construct for PIV3 not provided; construction not described. Recovery of recombinant virus not described.
Characteristics of chimeric virus with insert a- viable sequence b- specified length and strict adherence to the rule of six c- sequence at chimeric junctions	Complete description of DNAs and protocol; demonstration of successful recovery indicating authenticity of construct; confirmation of virus characteristics	Sequences of insert not provided; sequences of backbone not provided; junctions not specified, construction not described, recombinant virus not recovered

provided d- replication competent vector backbone, wild type nature of insert sequence e- construction of cDNA and expression plasmid		
Characteristics of full-length cDNA for attenuated PIV3 or chimeric virus a- viable sequence b- specified length ("rule of six") c- sequence at chimeric junctions d- construction of cDNA and expression plasmid e- replication competence of virus derived from cDNA	Complete description, demonstration of recovery and analysis of virus	Sequence of a full length cDNA from which attenuated PIV3 or attenuated virus not provided; construction not described, recombinant virus not recovered

19. Referring to Table 1, it is noted that the Belshe et al. application fails to provide an accurate sequence of a wild type PIV virus. This is a critical deficiency for describing and enabling the instantly claimed invention. Notably, PIV lacks a proof-reading polymerase and is known to have a high error rate. During cDNA cloning this high error rate is reflected in a relatively large number of sequence differences among clones, which are heightened by additional errors introduced during RT, PCR, and propagation in bacteria. A single point mutation in the 15.4 kb sequence can be sufficient to preclude recovery, and the identification and correction of potential errors presents a formidable challenge. The sequences described in Stoke's et al. and incorporated by Belshe et al. were later modified by the instant disclosure to correct errors, and the ultimate recovery of infectious virus verified that the presently described sequence is "viable". Thus, Belshe et al. rely on the previously reported sequence by Stokes et al, and there was no evidence at the time that this sequence, shown in the present

disclosure to be inaccurate, could have yielded a viable virus. Even if this untested, incorrect sequence were employed successful to obtain a recombinant virus, it was nonetheless unpredictable whether the sequence would specify a replication competent phenotype, i.e., a level of replication compatible with immunogenicity *in vivo*. Thus, Belshe et al. would not have been considered by the skilled artisan to enable recovery of a recombinant PIV3 nor a chimeric vaccine virus, since there was insufficient evidence that the reported sequence would yield these required results. Only the instant disclosure provides an authentic sequence of the full length PIV3 and its contiguous sequences in a plasmid with correct T7 promoter elements, T7 terminators, and hepatitis delta ribozyme. It is noteworthy that during the nearly seven years after the filing date of Belshe et al., Belshe and coworkers have apparently failed to recover any PIV from cDNA. In contrast, the instant disclosure provides a large, fully representative panel of recombinant viruses, including singly and multiply attenuated viruses and chimeric viruses. Among these recombinant viruses, PIV3 and PIV1 viruses and chimeric "vectors" have been constructed and demonstrated to be suitably attenuated and immunogenic to yield protection against PIV1, PIV2, and PIV3. Following these detailed teachings, our lab has progressed into clinical studies for PIV vaccine candidates recoverded from cDNAs.

20. In further reference to Table 1, Belshe et al. fails to describe or enable any specific sequence for an "insert" to yield a chimeric virus that would be compatible for efficient replication in a PIV3 backbone. Instead, Belshe et al. simply reference viral proteins, but do not specify any specific sequence of any insert, nor an insert length (columns 17– 18). Since there were many sequence errors existing in the literature, it would not have been possible to determine whether the chimeric viruses phrophetically reported by Belshe et al. would be viable, or, if viable, would possess a replication competent phenotype, i.e., a level of replication compatible with immunogenicity *in vivo*. In contrast, the PIV1 sequences used in the construction of chimeric cDNAs of the present invention to generate a PIV3-1 virus were obtained from a wild type PIV1 of know virulence for humans and, following insertion into the PIV3 backbone, yielded a chimeric virus with a verified wild type phenotype. The genes that encode the proteins alluded to by Belshe et al. include gene start sequences, a 5' non-coding region, coding region, 3' non-coding region, and gene-end sequence. The exact junctions of the sequences for the inserts referred to by Belshe et al. were not described and therefore one would not have known from the Belshe et al. description whether to include any of the extra-coding sequences or not. For example, the genes from any given virus contain transcription signals that differ from those of another virus, yet it is essential that the "transferred" gene be faithfully expressed in the new, heterologous viral backbone. This critical issue is not even addressed in the Belshe et al. specification.

In contrast, the instant disclosure provides exemplary descriptions of an insert, backbone, transcription signals and junctions to yield viable chimeric PIVs that are useful vaccine candidates.

21. Yet another critical deficiency of Belshe et al. that is resolved by the present disclosure relates to the length of the viral genome for production of recombinant PIVs. The length of the PIV genomes need to be an even multiple of six in order to recover authentic copies of virus containing the exact sequence in the cDNA. This "rule of six" reflects the association of each NP monomer with six nucleotides. If the genome does not conform to the rule of six, mutant viruses are recovered that have random mutations that correct the length. This factor adds a major aspect of uncertainty to the teachings of the Belshe et al. reference, which fails to appreciate the significance of the rule of six and the errors that would arise by failure to properly construct cDNAs in accordance with this requirement. In the instant disclosure, the exact lengths of a full length cDNA for PIV3 (number of nucleotides = 15462) and for PIV3-1 (number of nucleotides = 15516) are provided. This description in turn depended on the actual, successful recovery of recombinant PIVs and subsequent analysis and verification of the fidelity of the viral sequence and phenotype.

Table 2– Comparison of system used to recover virus from recombinant PIV3 or chimeric cDNA constructs

Requirements for successful rescue of recombinant chimeric PIV3 virus	Described in Murphy	Described in Belshe
Description of method used to recover infectious virus from chimeric cDNA including cell type, quantities of the full length genomic cDNA and support plasmids cDNA, source of T7 polymerase, compatibility of vaccinia virus expressing T7 with the virus to be recovered, method of isolating the recovered PIV	Exact transfection reaction described that yielded recombinant chimeric virus	Infectious virus not recovered –a method is described in very general terms and was not demonstrated to yield recombinant virus

22. In Table 1, above, the requirements for sequences of a full-length cDNA to successfully recover infectious, recombinant PIV are described. The specific methods used to recover infectious virus also need to be described to enable production of recombinant viruses from cDNAs. Systems to recover negative stranded RNA viruses such as PIV from cDNA are complicated and require a suitable cell capable of both successful transfection by plasmids and replication of the rescued virus. It should be noted that the recovery of infectious recombinant negative stranded RNA viruses is generally quite inefficient, such that out of 1,000,000 transfected cells, 10 or fewer cells actually produce virus (of course, once a recombinant virus is produced, it can then be propagated efficiently and evaluated like a biologically-derived virus). Particularly for a human pathogen such as PIV3, which does not grow rapidly *in vitro*, it is a formidable challenge to successfully produce and recover recombinant virus from cDNA. Our studies confirmed that the precise amount of the viral cDNA and support plasmid DNA was critical for initial recovery of recombinant PIV, and this factor was not appreciated by Belshe et al., who failed to even initiate a recovery system. As another example of inadequate guidance, Belshe et al. describe prohetically the use of cDNA expressing a genome sense RNA to recover virus (column 10, line 35). It is now known, however, that for technical reasons the recovery of virus from genome-sense RNA is relatively inefficient at best, and often unsuccessful. An optimal strategy employs a cDNA expressing a positive sense copy of the genome (called an antigenome). This guidance is clearly provided in present disclosure.

23. To enable production of a recombinant PIV from cDNA, a description of a system to promote expression of viral proteins from support plasmids and from a full-length cDNA that can form a functional transcriptase/replicase/genome complex is needed. A full description of this system is required, and notably lacking in the disclosure of Belshe et al. For example, the system described by Belshe et al. uses a replication competent vaccinia virus expressing T7 (Column 15 of Belshe), but it does not specify how a viable PIV virus would be recoverable in the presence of a vast excess of fully infectious, replication-competent vaccinia virus. It is unlikely that a low concentration of a recombinant PIV could be biologically separated from the replication-competent vaccinia. This is especially true since vaccinia virus is highly permissive for most cell types and is extremely difficult to fully neutralize with antibody. In contrast, in the methods described in the instant disclosure recognize and employ a replication deficient vaccinia virus (MVA-T7). This adaptation permitted the successful recovery of a recombinant PIV in the presence of the MVA-T7. Thus, Belshe et al. did not describe a system that would have been considered capable of successfully recovering recombinant PIV from cDNA, particularly attenuated (or attenuated, chimeric) viruses having further restrictions on replication.

24. The complexities and uncertainties that we had to overcome to achieve successful recovery of PIV from cDNA is further evinced by the extensive work involved in the recovery of other infectious recombinant negative strand RNA viruses. The general strategy that has proven successful is to reconstruct the viral nucleocapsid intracellularly from plasmid-expressed components. This is based on the idea that the nucleocapsid, i.e. the genome complexed with the nucleocapsid and polymerase proteins, constitutes the minimum unit of infectivity, a concept that dates back at least as far as 1967 (Brown et al. 1967 J. Virol. 1:368). In 1990, Ballart et al (Ballart et al 1990 EMBO J. 9:379) constructed a complete cDNA expressing the genome of measles virus under the control of a T7 promoter and reported the recovery of recombinant measles virus by complementation of this synthetic genome with intracellularly-expressed measles virus proteins. Although this report proved to be erroneous and was retracted (Eschle et al, 1991 EMBO J. 10:3558), this work outlined important general concepts for recovery. However, it is noteworthy that, despite considerable research effort on this high profile project, successful recovery of recombinant measles virus was not reported until December, 1995 (Radecke et al, 1995 EMBO J. 14:5773), a 5- to 6-year gap that reflects the formidable technical and conceptual challenges that must be met to achieve a successful recovery system. During that period, there was genuine concern that successful recovery of any negative strand virus might not be feasible. Thus, the successful recovery of recombinant rabies rhabdovirus in 1994 was a major milestone (Schnell et al 1994 EMBO J. 13:4195). However, it was not clear whether this would be successful with

paramyxoviruses, which have substantially greater genome size and complexity, more complex sets of protein products, and poorer growth and stability. In work with a second virus, the highly efficient rhabdovirus vesicular stomatitis virus (VSV), it was shown in 1990 that plasmid-expressed proteins could support a biologically derived nucleocapsid (Pattnaik et al, 1990 J. Virol. 64:2948), but two more years were required to develop the capability to express a defective interfering particle from cDNA (Pattnaik et al, 1992 Cell 69:1011). Three more years were required to express complete infectious recombinant virus (Lawson et al 1995 Proc. Natl. Acad. Sci. USA 92:4477; Whelan et al, 1995 Proc. Natl. Acad. Sci. USA 92:8388), which also was viewed as a major achievement (Roberts and Rose 1998 Virology 247:1). The work with the rhabdoviruses rabies and VSV involved unexpected requirements, such as the need to express the genome in positive sense form, the need to avoid structures causing early termination by the T7 RNA polymerase, and the need to reduce the background of vaccinia virus. In many instances, recovery depended on methods that could not be applied generally to other viruses, such as removal of the vaccinia virus background by filtration (Schnell et al 1994 EMBO J 13:4195, Lawson et al, ibid), which could not be applied to paramyxoviruses because of their large size and hence necessitated the development of alternative strategies. Studies in other nonsegmented negative stranded viruses illustrate still other unexpected requirements, such as the need to express an additional protein, the M2-1 protein, to achieve successful recovery of human respiratory syncytial virus (Collins et al, 1999, Virology 259:251). This brief survey of the literature embraces only to a subset of studies I know to have been undertaken in large numbers of labs across the globe seeking to recover negative stranded RNA viruses from cDNA. Many of those labs that never came close to successful recovery, thus their efforts have gone unreported. In summary, myriad challenges have persisted in the art to development of a successful recovery system for PIV. These challenges underscore the deficiencies of Belshe et al., who provide only vague, generic concepts without documentary experimentation nor demonstration of a feasibile recovery system for PIV. At the same time, the slow-developing state of the art, and the high level of unpredictability in the field, emphasize the unexpected nature of results provided within the instant disclosure.

Table 3 – Characteristics of recovered PIV3 or recombinant chimeric PIV

Characteristics of PIV3 or chimeric virus recovered from full-length cDNA	Described in Murphy	Described in Belshe et al.
Viable virus that is recovered from wild	Viruses recovered and wild	Recombinant wild type

type PIV3 cDNA and from cDNA with backbone of wild type PIV3 containing substitution of wild type PIV1 HN and F for PIV3 HN and F and is replication competent and immunogenic in vivo is characterized for properties.	type phenotype demonstrated	or chimeric virus not recovered and thus properties could not be determined
Viable attenuated virus is recovered from PIV3 cDNA containing attenuating mutations and from cDNA with backbone of attenuated PIV3 containing substitution of wild type PIVi HN and F for PIV3 HN and F	Virus recovered and attenuation, immunogenicity, and efficacy demonstrated	Recombinant attenuated PIV3 or chimeric virus not recovered and thus properties could not be determined

25. Although Belshe et al. show that it is facile to prophetically describe a method for recovering recombinant PIV from cDNA, the actual successful recovery of recombinant PIV for use a vaccine is far more complicated than indicated by the cited reference. The properties of the virus that make it a successful vaccine candidate must be described in detail in a representative assemblage of recombinant species, as provided by the instant disclosure. There are three possible consequences that can occur when one attempts to recover a wild type PIV3 or a chimeric recombinant virus from cDNA: (1) a recombinant virus is recovered that replicates to levels characteristic of wild type virus or indicative of attenuation; (2) a recombinant virus is recovered that contains one or more inadvertent and unknown sequence errors that render it defective in any of a number of ways; and (3) virus is not recovered, due either to one or more lethal sequence errors or some deficiency in the recovery strategy or conditions. When one introduces mutations into such a cDNA intended to attenuate the virus and thereby to render it useful as a vaccine candidate, at least four outcomes are possible: (1) one can increase the virulence of the virus; (2) one can incompletely attenuate the virus; (3) one can achieve a satisfactory level of attenuation such that a virus can be used as a vaccine; and (4) one can over-attenuate a virus or render it non-viable. The examples provided in the instant specification fulfill criterion 3 by providing a representative assemblage of recombinant viruses that are suitably attenuated for development as vaccine agents. In contrast, the disclosure of Belshe et al. fails to achieve any of the foregoing possibilities--by virtue of its failure to describe and enable a cDNA construct encoding a

recombinant PIV (see Table 1), for failing to recover infectious virus from cDNA (Table 2), and for the lack of testing and characterization of an infectious, recombinant virus (Table 3).

26. In fact, the Belshe et al. specification provides only a limited description concerning the use of a plasmid expressing a wild type PIV3 L protein to enhance replication of a JScp45 virus at a restrictive temperature of 39.5°C. This limited disclosure does not provide a reasonable scientific basis for the speculation by Belshe et al. that the L gene of cp45 possesses mutations that might be useful in a recombinant PIV vaccine virus derived from cDNA. The virus recovered by Belshe et al. after complementation with the L-encoding plasmid at the restrictive temperature was not changed or modified in any manner as contemplated by Applicants' disclosure. No cDNA constructs were designed and produced from which PIV3 wild type viruses could be recovered, and certainly no new constructs or recombinant viruses bearing a chimeric genome or antigenome, and/or specific, attenuating mutations were described or enabled. The absence of such disclosure in the Belshe et al. reference negates any "reasonable expectation for success" to achieve the presently claimed invention in either its independent or dependent aspects. This is especially clear when the particular results provided by the instant disclosure are appreciated, namely that it was shown to be possible to construct a panel of recombinant PIVs, including singly and multiply attenuated and chimeric viruses, from cDNA that are suitably attenuated and immunogenic for development as vaccine candidates.

27. Concerning the issue of enablement, the foregoing discussion clearly establishes that the application provides extensive description, guidance, and working examples that teach the skilled artisan how to make and use recombinant PIVs from cDNA in a manner that is reasonably correlated with the full breadth of the claims. Numerous recombinant PIVs are described and tested in accepted model systems. For example, the instant disclosure details five attenuating mutations from the cp45 mutant that are identified, incorporated, and directly characterized in a recombinant PIV of the invention. Three of these mutations, identified in three different genes (C, F, and L), were shown to specify temperature sensitive attenuating mutations, while two others were demonstrated to specify non-ts attenuating mutations. Through the use of our novel PIV recovery system, the ability of these mutations to independently confer the property of attenuation on a recombinant virus in the absence of other cp45 mutations was proven. These studies fully evince the general usefulness of these mutations for attenuating recombinant vaccine viruses, including chimeric recombinant vaccine viruses, of the invention. At the same time, these studies clearly establish that a skilled artisan, following the teachings of the instant disclosure, will be enabled to identify additional useful mutations for incorporation within

recombinant PIV vaccine viruses of the invention, without undue experimentation. In particular, the successful recovery of a representative assemblage of useful recombinant PIV vaccine candidates shown here provides strong motivation and clear, detailed guidance to render any such experimentation as needed to obtain additional species within the generic scope of the instant claims "reasonable" and attended by a high expectation of success. That certain species may be less optimal than others, or even inoperable, does not negate the broad utility and scope of the invention in this context. The poorly developed state of the art and high degree of unpredictability that existed prior to the current invention is no longer extant. On the contrary, these barriers have been lowered sufficiently that the skilled artisan, availed of the teachings of the instant specification, can practice the invention throughout its scope without such extensive and/or uncertain experimentation that would be considered "undue" or unreasonable.

28. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that I make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize validity of the application or any patent issuing thereon.

Date: 8/26/02 By: Brian R. Murphy MD

Brian R. Murphy, M.D.

CURRICULUM VITAE

Name: Brian R. Murphy, M.D.

Date and Place of Birth: July 17, 1942; New York, New York

Social Security Number: 128-34-5897

Citizenship: United States

Marital Status: Married; two children

Address:

Home:
5410 Tuscarawas Road
Bethesda, MD 20816
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50 South Drive MSC 8007
Bethesda, MD 20892-8007
Tele.: (301) 594-1616
FAX: (301) 496-8312
FAX: (301) 480-5033
E-mail: bm25f@nih.gov

Education:

June, 1960	Graduated from High School
June, 1964	B.A., Wesleyan University, Connecticut
June, 1969	M.D., University of Rochester, School of Medicine

Brief Chronology of Employment:

1966 - 1967	Student Fellow, School of Medicine, University of Rochester, Department of Microbiology
1969 - 1970	Internship, Stanford University Hospital, Palo Alto, California
1970 - 1983	Research Associate, Laboratory of Infectious Diseases, NIAID, NIH, Bethesda, Maryland
1983 - 2001	Head, Respiratory Viruses Section, Laboratory of Infectious Diseases, Nationa

2001- present	Co-Chief, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland	

Military Service:

1970 - 1998	United States Public Health Service

Societies:

Alpha Omega Alpha
American Society for Microbiology
Infectious Diseases Society
American Society for Virology

U.S. Patents:

Title:	TEMPERATURE-SENSITIVE RECOMBINANT MUTANT VIRUSES AND A PROCESS FOR PRODUCING SAME
Inventors:	Robert M. Chanock, Brian R. Murphy
Patent No.	3,992,522
Date:	November 16, 1976
Title:	USE IN AN ANIMAL HOST AND PRECURSORS FOR VACCINES UTILIZING AVIAN-HUMAN REASSORTANTS TO COMBAT INFLUENZA A
Inventors:	Brian R. Murphy, Robert M. Chanock, Robert G. Webster, Virginia S. Hinshaw
Patent No.	4,552,757
Date:	November 12, 1985
Title:	HUMAN USE OF AVIAN-HUMAN REASSORTANTS AS VACCINES FOR INFLUENZA A VIRUS
Inventors:	Brian R. Murphy, Robert M. Chanock, Robert G. Webster, Virginia S. Hinshaw
Patent No.	4,552,758
Date:	November 12, 1985
Title:	HUMAN NEUTRALIZING MONOCLONAL ANTIBODIES TO RESPIRATORY SYNCYTIAL VIRUS
Inventors:	Dennis R. Burton, Carlos F. Barbas, III, Robert M. Chanock, Brian R. Murphy, James E. Crowe, Jr.
Patent No.	5,762,905
Issued:	June 9, 1998
Title:	ATTENUATED RESPIRATORY SYNCYTIAL VIRUS VACCINE COMPOSITIONS
Inventors:	Brian Murphy, Robert Chanock, James Crowe, Jr., Mark Connors
Patent No.:	U.S. 5,922,326
Date:	July 13, 1999

Title: PRODUCTION OF ATTENUATED RESPIRATORY SYNCYTIAL VIRUS VACCINES FROM CLONED NUCLEOTIDE SEQUENCES
Inventors: Brian R. Murphy, Peter L. Collins, Stephen S. Whitehead, Alexander A.Bukreyev, Katalin Juhasz, Michael N. Teng
Patent No.: 5,993,824
Issued: Nov. 30, 1999

Title: IMMUNOGENIC COMPOSITIONS COMPRISING COLD-ADAPTED ATTENUATED RESPIRATORY SYNCYTIAL VIRUS MUTANTS
Inventors: Brian Murphy, Robert Chanock, James Crowe, Jr., Mark Connors, K-H L Hsu, A.R. Davis, M.D. Lubeck, B.H. Selling
Patent No.: 6,284,254 B1
Issued: Sept. 4, 2001

Member of Editorial Board and/or Reviewer for the Following Journals:

Reviewer of manuscripts for the following journals:
Antiviral Research
Archives of Virology
Clinical Microbiological Review
Journal of Clinical Investigation
Journal of Clinical Microbiology (editorial board),
Journal of Experimental Medicine
Journal of General Virology
Journal of Infectious Diseases
Journal of Immunology
Journal of Virology (editorial board)
New England Journal of Medicine
Proceedings of the National Academy of Sciences USA
Science
Vaccine
Virology

Honors and Other Special Scientific Recognition:

Edwin G. Strasenburgh Award, Rochester Academy of Medicine, 1967, 1969
Doctor of Medicine, with distinction in research
Consultant, World Health Organization at Meeting of Directors of WHO Respiratory Virus and Enterovirus Reference Center, April 16-19, 1973
Participant in a Symposium on Vaccination Against Influenza, London, April 1975
Invited speaker at ASM Conference on Myxovirus Genetics, Tampa, Florida, March 6-8, 1977
Invited participant at the Directors of the WHO Collaborating Centers for Virus Reference and Research Meeting, June 6-10, 1977
Invited participant in the International Association for Biological Standardization Meeting on Influenza Vaccines in Geneva, Switzerland, June 1977
Recipient of the PHS Commendation Medal, 1977

Invited speaker at the Symposium on the Advances in Vaccination against Virus Diseases in Bern, Switzerland, June 1978
Invited speaker, Royal Society Symposium on Influenza Virus Genetics, London, England, February 21 and 22, 1979
Invited speaker, New York Academy of Sciences Conference on Genetic Variation of Viruses, November, 1979
Chairman, ASM Seminar on Viral Vaccines of the Future, Miami, Florida, May 1980
Consultant on Influenza Vaccines, World Health Organization, November 1980
Invited speaker, ICN-UCLA Conference on the Genetic Variation of Influenza Viruses, Salt Lake City, Utah, March 1981
Invited speaker, Vaccination Against Influenza; T or B Cell Immunity, Oxford England, March 1982
Invited speaker, "Molecular Virology and Epidemiology of Influenza" (in celebration of 50 years of research on the Influenza Viruses) Hampstead, London, September 1983
Invited speaker, Cold Spring Harbor Conference on "Modern Approaches to Vaccines," Cold Spring Harbor, New York, September 1983
Keynote speaker, Eastern Chapter of American Society of Microbiology, Philadelphia, Pennsylvania, February 1985
Recipient of PHS Meritorious Service Medal, May 1985
Editorial board, *Journal of Clinical Microbiology*, January 1986-present
Convenor, American Society for Microbiology, "Viral Vaccines: Development and applications," Washington, DC, March 26, 1986
Consultant to U.S. Army Medical Research Institute of Infectious Diseases, "VEE Vaccines for Man," Fort Detrick, Maryland, December 1986
Co-inventor, United States Patent (number pending) Temperature sensitive reassortant viruses and vaccine against equine influenza, February 1987
Invited lecturer at Johns Hopkins School of Medicine, University of Maryland at College Park, and University of Maryland School of Medicine, Baltimore, MD and Mount Sinai Medical Center, and Uniformed Services University of the Health Sciences, 1987-1990.
Consultant, World Health Organization, 1987
State-of-the-Art lecture at the American Society of Virology meeting, Chapel Hill, North Carolina, June 1987
Chairman, Vaccines II session, American Society of Virology meeting, Chapel Hill, North Carolina, June 1987
Invited speaker at the Orthomyxovirus Symposium held at the VII International Congress of Virology, Edmonton, Canada, August 1987
Invited speaker at the "Oral Immunization Symposium" held in Birmingham, Alabama March 21, 1988
Invited speaker at Stanford University's lecture series on "Molecular and Genetic Medicine - Molecular Responses to Virus Infection" on May 2, 1988
Recipient of the United States Public Health Service Outstanding Service Medal, June 6,1988.
Invited to present summary of the Vaccines 88 meeting held at Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, September, 1988
Appointed to the World Health Organization Steering Committee on Respiratory Viruses, 1988-1994.
Editorial Board, *Journal of Virology*, January 1, 1989 to 1994
Invited speaker at Conference on Emerging Viruses: Evolution of Viruses and Viral Diseases, sponsored by NIAID, Fogarty International Center, and the Rockefeller University, Washington, DC, May 1-3, 1989

Chairman of session on Vectors and Vaccines at a Symposium on Respiratory Virus Vaccine Development, sponsored by the World Health Organization, Washington, DC, May 1, 1989

Appointed Chairman of the World Health Organization Steering Committee on Respiratory Viruses and Measles, August 1989-1992.

Guest lecturer at the Department of Pediatrics at Vanderbilt University, July 18, 1989

Guest lecturer at the State University of New York at Buffalo, New York, September 16, 1989

Guest lecturer at the University of Maryland, School of Medicine, Department of Pediatrics, November 1989

Guest lecturer at Johns Hopkins University Department of Immunology, February 5, 1990

Chairman of session on Virology, Vaccines 89 symposium held at Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, September 1989

Invited to present lecture for the plenary session of the VIth International Conference on Comparative and Applied Virology, Baniff, Alberta, Canada, October 15-21, 1989

Invited to review the Discovery Program of the Biotechnology and Microbiology Division of Wyeth-Ayerst Research, November 9-10, 1989

Visiting Research Professor at Children's Hospital National Medical Center, April 2, 1990

Co-organizer of WHO meeting on "New approach to measles virus vaccine" May 25-26, 1990

Invited to present lecture "RSV Vaccines" University of Massachusetts Medical School, Worcester, MA, October 3, 1990

Co-organizer of meeting on RSV vaccines, "Animal Models of RSV." Foundation Merieux, Annecy, France, October 23-25, 1990

Guest lecturer at the University of Maryland, October 1990-1993; Foundation for Advancement of Sciences at NIH course on Virology, Uniformed Services University of the Health Services, January, 1991; NIAID Immunology Course, February, 1991; NIAID Program "Introduction to Biomedical Research," February 1991.

Invited to give seminar "Current status of live attenuated influenza vaccines" January 10-11, 1991. Department of Immunology and Medical Microbiology, University of Florida.

Invited to present lecture "Influenza Viruses" to Department of Immunology and Infectious Diseases, Johns Hopkins University, February 13, 1991.

Invited to present a talk and chair a discussion section at the Poxvirus Vectors for HIV Vaccines held at NIH on August 22, 1991 on "Experiments to be conducted to evaluate safety/immunogenicity."

Invited speaker, "General Overview of Viral Vaccine Development," presented at conference entitled "Genetically Engineered Vaccines: Prospects for Oral Disease Prevention," National Institute of Dental Research, November 6, 1991.

Invited speaker, "The Use of Chimpanzees in Respiratory Virus Research," presented at a conference on "Chimpanzee Conservation and Public Health: Environments for the Future, sponsored by Diagnon Corporation, Rockville, MD, November 11, 1991.

Invited speaker, "The Development of Live Attenuated Influenza A Virus Vaccines," for NIAID Grand Rounds, National Institutes of Health, November 20, 1991.

Organizer of the WHO Meeting of RSV and PIV3 Vaccines, Geneva, Switzerland, April 21-22, 1992.

Invited participant, Buffalo Conference on Microbial Pathogenesis, Buffalo, NY, April 29,1992.

Invited lecturer, Case Western Reserve University Institute of Pathology, Immunology Seminar Series, Cleveland, Ohio, May 5, 1992.

Recipient of Federal Laboratory Consortium Award on Technology Transfer for 1992.

Chairman of session on Vaccines, The Annual Meeting of the American Society of Virology, Ithaca, NY, July 1992.
Scientific Advisory Board, AVIRON, Palo Alto, CA, 1992 - 1993.
Member of NIAID Animal Care and Use Committee, 1989 - 1993.
Member of NIAID Technology Evaluation Advisory Committee, 1991 - Present.
Member of NIH ACUC Containment Housing for Research Animals Subcommittee, 1992.
Member of NIH Interagency Animal Model Committee (Infectious Diseases Subcommittee).
Chairman, Session on Bacteriology and Parasitology at the Cold Spring Harbor Meeting on "Modern Approaches to New Vaccines," September 16-20, 1992.
Chairman, Wyeth Ayerst-LID/NIAID Cooperative Research and Development Agreement Committee on the Development of Live Attenuated Respiratory Syncytial Virus Vaccines, 1992-Present.
Speaker at the NIH Clinical Center Grand Rounds on "Vaccines for Influenza," September 23, 1992.
Invited speaker, Johns Hopkins Pediatric Vaccine Seminar Series.
Member, NIH Institutional Biosafety Committee, 1993 - 1997.
Invited speaker, Keystone Symposia - Molecular Immunology of Virus Infections, Taos, NM, March 1993.
Invited speaker at WHO-NIAID meeting, Bethesda, MD, "Protective and Disease Enhancing Immune Response to RSV," May 1993.
Invited speaker at the American Society of Virology Satellite Symposium on Medical Virology on "Immunobiology of RSV Infection and Immunization," July, 1993, Davis, CA.
Workshop Co-chairman on Respiratory Viruses, IXth International Congress of Virology, Glasgow, August 1993.
Consultant for Genetic Therapies, Inc., September, 1993.
Invited speaker, St. Jude's Children's Hospital Virology Seminar Series, "Immunobiology of RSV," October 1993.
Organizer of WHO Meeting on Development of Vaccines Against Diseases Caused by RSV and PIV3, Nyon, Switzerland, March 27, 1994.
Invited speaker, Experimental Biology 94th Symposium, *Mucosal Vaccines: Recent Developments in Design and Human Analysis*, talk entitled "Mucosal Immunity to Respiratory Viral Infections," Anaheim, California, 1994.
Member, Search Committee for Chief, Division of Viral Products, FDA, CBER, 1994.
Invited speaker, Australian Society for Microbiology, presented the Bazely Oration entitled "Immunization against Respiratory Viruses," Melbourne, Australia, September 26, 1994.
Invited speaker, Australian Society for Microbiology Symposium on "Respiratory Viruses: Epidemiology and Control" talk entitled "Vaccines for Respiratory Syncytial Virus and Parainfluenza Virus Type 3," Melbourne, Australia, September 29, 1994.
Chairman of Session on "Virology," at the Meeting "Molecular Approaches to the Control of Infectious Diseases," Cold Spring Harbor, NY, October 5-9, 1994.
Scientific Advisory Board, Albert B. Sabin Vaccine Foundation, 1994.
Invited speaker, The Eastern Pennsylvania Branch of the American Society for Microbiology Symposium on "Vaccines: Preventive Strategies for the 21st Century." Talk entitled: "The Development and Evaluation of Live Attenuated Respiratory Syncytial Virus Vaccines," Philadelphia, PA, December 8-9, 1994.
Invited speaker, Keystone Symposia on Molecular Aspects of Viral Immunity. Talk entitled "Progress Toward the Development of a Live Attenuated Respiratory Syncytial Virus (RSV) Vaccine," Keystone, CO, January 16-23, 1995.

Co-chairperson of a Workshop on "Retroviral Screening, Sensitivity and Specificity" at FDA/CBER Meeting on "International Scientific Conference on Viral Safety and Evaluation of Viral Clearance from Biopharmaceutical Products" held at NIH, Bethesda, MD, June 14-16, 1995.

Presented "State-of-the-Art" Minilecture on "New Developments in Respiratory Virus Vaccines" at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 19, 1995.

Co-Organizer of "Workshop III -- Vaccines Against Respiratory Diseases" and Presenter of a lecture on "Two live attenuated parainfluenza virus type 3 (PIV3) candidate vaccines are safe, genetically stable, and immunogenic in seronegative infants and young children" at "Vaccines, One Hundred Years After Louis Pasteur," Institute Pasteur, Paris, France, September 24-28, 1995.

Invited speaker, NIH Grand Rounds on Influenza Virus Vaccines, November 1, 1995.

Invited speaker, Department of Microbiology and Immunology of the University of North Carolina at Chapel Hill Seminar Series. Talk entitled: "New Genetically Engineered Vaccines for Influenza A Viruses" November 16, 1995.

Invited speaker, On Pandemic Influenza -- Confronting a Re-Emergent Threat. Talk entitled: "Live Virus Vaccines" December 11-13, 1995.

NIAID Principle Investigation on NIH-Wyeth Lederle Pediatric Vaccines CRADA on Parainfluenza Virus type 3 vaccine development.

Member of NIAID Promotions and Tenure Committee, 1996 - 1999.

Invited lecturer on Influenza Virus Vaccine Development for a course "Biologic Basis of Vaccine Development" at the Johns Hopkins School of Hygiene and Public Health, Baltimore MD, May, 3, 1996.

Invited lecturer on Progress with RSV and Parainfluenza Virus Vaccine Development at the ATCC Seminar

Co-organizer of WHO-NIAID Conference on RSV and PIV3 Vaccines held at NIH, Sept 30-Oct 1, 1996.

Invited to present a talk entitled "Vaccine Viruses of the Future" at the 1996 Medical Scientific Day Confere

Appointed to the Malaria Vaccines Development Unit Scientific Advisory Board, 1997.

Co-Organized the NIH-WLVP RSV-PIV3 CRADA Meeting in Pearl River, NY on February 11 -12, 1997.

Co-Organized the NIH-WLVP RSV-PIV3 CRADA Meeting in Pearl River, NY on February 22 -24, 1998.

Invited participant in workshop on the "Appearance of H5N1 in humans" sponsored by the Institute of Immu

Invited speaker at Conference on Mucosal Immunology and Medicine in St. Lucia on March 17-18, 1998. Talk entitled: "Paramyxovirus vaccines for the early 21st century."

Invited speaker at a workshop on "Structure and Replication of Negative Strand RNA Viruses" held at North

Invited speaker at the Research Triangle Virology Group Meeting in Raleigh, NC on September 9, 1998. Tal

Participant at an NIAID meeting on Influenza Virus Pandemic Planning on September 29-30, 1998, in Rock

Invited speaker, International Symposium on Influenza and other Respiratory Viruses, talk entitled "Molecular approaches to the generation of RSV and PIV vaccines," Dec. 4-6, 1998, Maui, Hawaii.

Invited speaker. Vaccine Research Center Discussion Group. Lecture entitled "Molecular approaches to the generation of RSV and PIV vaccines," Jan. 26, 1999, NIH, Bethesda, Maryland.

Invited speaker; Rudi Kasel Memorial Lecture. Talk entitled "Molecular approaches to the development of

Invited speaker; Keystone Symposia on Molecular Approaches to Human Viral Vaccines. Talk entitled "Parainfluenza: Traditional versus molecular approaches to live virus vaccine development," April 12-17, 1999.

Invited to participate as a State-of-the-Art lecturer, 18th Annual Meeting of the American Society for Virology, Amherst, Massachusetts. Talk entitled "Molecular approaches to developing vaccines to parainfluenza viruses," July 10-14, 1999.

Invited to present a lecture on "Live attenuated virus vaccines: Preclinical Aspects" at the "II International Symposium on Influenza and Other Respiratory Virus Vaccines" held in Grand Cayman, Cayman Islands, December 10-12, 1999. Member of the Scientific Advisory Committee for the meeting.

Invited to participate in the NIH "Clinical Center Roundtable" broadcast on "Frontiers in Immunization - New and Improved Vaccines," December 17, 1999.

Invited speaker, "The Third Annual Conference on Vaccine Research." Talk entitled "Respiratory Syncytial Virus Vaccines." May 2, 2000,Washington DC.

Invited speaker at a symposium entitled "Pediatric Immunization. The Next Steps." Talk entitled "Recent Development of Live Attenuated Strains of Parainfluenza and Respiratory Syncytial Virus Vaccines." May 18, 2000, Chapel Hill, North Carolina.

Invited convener at the American Society of Virology Workshop #7, Paramyxoviruses and Bornaviruses: Replication. July 8, 2000, Fort Collins, Colorado.

Member of Scientific Advisory Committee for the "III International Symposium on Respiratory Viral Infections," December 1-3, 2000 in St. Lucia, Windward Island. Presented talk entitled "What are the diseases requiring vaccines and what is available."

Invited speaker on "Live viral (parainfluenza) vectored measles vaccines" at meeting entitled "Consultation of new measles virus vaccine candidates" on Mar. 22, 2001, Johns Hopkins University, Baltimore, MD.

Invited participant or the ACIP Influenza Working Group Meeting in Decatur, GA, May 9-10, 2001.

Invited speaker at ASM Colloquium on Live Engineered Vaccines at American Society for Microbiology 101th General Meeting, Orlando, Florida, May 22, 2001. Talk entitled "Molecular approaches to making live attenuated flavivirus vaccines".

Invited participant, NIAID Reverse Genetics Workshop, Georgetown, Washington, D.C. July 9-10, 2001.

Invited Consultant to the FDA for the Vaccines and Related Biological Products Advisory Committee Meeting for evaluation of the "Influenza Virus Vaccine, Trivalent, Types A and B, Live, Cold-Adapted in Rockville, MD on July 26-27, 2001. Presented talk concerning "Overview of Development of Cold-adapted, Live Attenuated Influenza Vaccines; Basis of Attenuation; and Potential for Reassortment with Wild-type Viruses in Nature.

Invited speaker, "Influenza Viruses – Medicine for the Public", NIH, Oct. 30, 2001.

Invited panel participant, NIAID Blue Ribbon Panel on Terrorism and its Implications for Biomedical Research, NIH, Feb. 4-5, 2002.

BIBLIOGRAPHY

1. **Murphy BR**, Glasgow LA. Factors modifying host resistance to viral infection. III. Effect of whole body X-irradiation on experimental encephalomycarditis virus infection in mice. *J Exp Med* 1968;**127**:1035-1052.

2. **Murphy BR**, Glasgow LA. Factors modifying host resistance to viral infection. I. Effect of immunosuppressive drugs on experimental infection of mice with encephalomycarditis virus. In Hobby GL, ed. *Antimicrobial Agents and Chemotherapy*. Ann Arbor, MI: American Society of Microbiology 1969;661.

3. **Murphy BR**, Glasgow LA. The antiviral activity of 3, 4-dehydro-1-isoquinolineacetamide hydrochloride on Columbia SK virus infection in mice and tissue culture. *Ann NY Acad Sci* 1970;**173**:225-273.

4. **Murphy BR**, Kasel JA, Chanock RM. Association of serum anti-neuraminidase antibody with resistance to influenza in man. *N Engl J Med* 1972;**286**:1329-1332.

5. **Murphy BR**, Chalhub EG, Nusinoff SR, Chanock RM. Temperature-sensitive mutants of influenza virus. II. Attenuation of *ts* recombinants for man. *J Infect Dis* 1972;**126**:170-178.

6. **Murphy BR**, Chalhub EG, Nusinoff SR, Chanock RM. Temperature-sensitive mutants of influenza virus. III. Further characterization of the *ts*-1[E] influenza A recombinant (H3N2) virus in man. *J Infect Dis* 1973;**128**:479-487.

7. **Murphy BR**, Baron S, Chalhub EG, Uhlendorf CP, Chanock RM. Temperature-sensitive mutants of influenza virus. IV. Induction of interferon in the nasopharynx by wild-type and a temperature-sensitive recombinant virus. *J Infect Dis* 1973;**128:**488-493.

8. Parrott RH, Kim HW, Arrobio JO, Hodes DS, **Murphy BR**, Brandt CD, Camargo E, Chanock RM. Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race, and sex. *Am J Epidemiol* 1973;**98**:289-300.

9. **Murphy BR**, Hodes DS, Nusinoff SR, Spring-Stewart S, Tierney EL, Chanock RM. Temperature-sensitive mutants of influenza virus. V. Evaluation in man of an additional *ts* recombinant virus with a 39°C shutoff temperature. *J Infect Dis* 1974;**130**:144-149.

10. Richman DD, **Murphy BR**, Tierney EL, Chanock RM. Specificity of the local secretory antibody to influenza A virus infection. *J Immunol* 1974;**113**:1654-1656.

11. Chanock RM, Richman DD, **Murphy BR**, Spring SB, Schnitzer TS, Richardson LS. Current approaches to viral immunoprophylaxis. In Notkins AL, ed. *Viral Immunology and Immunopathology*. New York: Academic Press 1975;291-316.

12. **Murphy BR**, Richman DD, Chalhub EG, Uhlendorf CP, Baron S, Chanock RM. Failure of attenuated temperature-sensitive influenza A (H3N2) virus to induce heterologous interference in humans to parainfluenza type 1 virus. *Infect Immun* 1975;**12**:62-68.

13. **Murphy BR**, Spring SB, Richman DD, Tierney EL, Kasel J, Chanock RM. Temperature-sensitive mutants of influenza virus. VII. Transfer of the *ts*-1[E] lesions to a wild-type influenza A virus with the HON1 surface antigens. *Virology* 1975;**66**:533-541.

14. Richman DD, **Murphy BR**, Cline WC, Alling DW. Determination of influenza virus neuraminidase inhibition titres. *Bull WHO* 1975;**52**:233-234.

15. Richman DD, **Murphy BR**, Spring SB, Coleman MT, Chanock RM. Temperature-sensitive mutants of influenza virus. IX. Genetic and biological characterization of *ts*-1[E] lesions when transferred to a 1972 (H3N2) influenza A virus. *Virology* 1975;**66**:551-562.

16. Spring SB, Nusinoff SR, Mills JV, Richman DD, Tierney EL, **Murphy BR**, Chanock RM. Temperature-sensitive mutants of influenza virus. VI. Transfer of *ts* lesions from the Asian subtype of influenza A virus (H2N2) to the Hong Kong subtype (H3N2). *Virology* 1975;**66**:522-532.

17. Spring S, Nusinoff S, Tierney EL, Richman DD, **Murphy BR**, Chanock RM. Temperature-sensitive mutants of influenza virus. VIII. Genetic and biological characterization of *ts* mutants of influenza virus A (H3N2) and their assignment to complementation groups. *Virology* 1975;**66**:542-550.

18. Douglas RG Jr, Bentley DW, Betts RR, Zaky DA, Roth FK, **Murphy BR**. Evaluation of a temperature sensitive influenza virus in elderly and chronically ill subjects. *Am Rev Respir Dis* 1976;**113**:293-300.

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